SELECTIVITY AND MOLECULAR MECHANISMS OF TOXICITY

EDITED BY
F. DE MATTEIS
E.A. LOCK

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F. De MATTEIS

MRC Toxicology Unit
Carshalton, Surrey SM5 4EF, UK

and

E. A. LOCK

ICI plc Central Toxicology Laboratory
Alderley Park, Macclesfield, Cheshire SK10 4TJ, UK

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Contents

The Contributors

W. N. Aldridge
Medical Research Council
Toxicology Unit
Carshalton
Surrey SM5 4EF
UK

F. Berends
Medical Biological Laboratories – TNO
Lange Kleiweg 139
P.O. Box 45
2280 AA Rijswijk
The Netherlands

A. P. DeCaprio
Wadsworth Center for Laboratories and Research
New York State Department of Health
Empire State Plaza
Albany, New York
NY 12201
USA

F. De Matteis
Medical Research Council
Toxicology Unit
Carshalton
Surrey SM5 4EF
UK

D. Dinsdale
Medical Research Council
Toxicology Unit
Carshalton
Surrey SM5 4EF
UK

D. Henschler
Institute of Pharmacology and Toxicology
University of Würzburg
Versbacher Strasse 9
8700 Würzburg
West Germany

M. K. Johnson
Medical Research Council
Toxicology Unit
Carshalton
Surrey SM5 4EF
UK

P. Jenner
Institute of Psychiatry
and King's College Hospital Medical School
Denmark Hill
London SE5 8AF
UK

E. A. Lock
Central Toxicology Laboratory
Imperial Chemical Industries plc
Alderley Park
Macclesfield
Cheshire SK10 4TJ
UK

L. L. Smith
Central Toxicology Laboratory
Imperial Chemical Industries plc
Alderley Park
Macclesfield
Cheshire SK10 4TJ
UK

C. D. Marsden
Institute of Psychiatry
and King's College Hospital Medical School
Denmark Hill
London SE5 8AF
UK

F. Stirpe
Instituto di Patologia Generale dell'Università
di Bologna
I–40126 Bologna
Italy
and
Drug Targeting Laboratory
Imperial Cancer Research Fund
London WC2A 3PX
UK

B. Nemery
Medical Research Council
Toxicology Unit
Carshalton
Surrey SM5 4EF
UK

Present address:
Université Catholique de Louvain
Unité de Toxicologie Industrielle et
Médecin du Travail
Clos Chappelle-aux-Champs 30–54
1200 Brussels
Belgium

R. D. Verschoyle
Medical Research Council
Toxicology Unit
Carshalton
Surrey SM5 4EF
UK

A. H. Penninks
Department of Veterinary Pharmacology,
Pharmacy and Toxicology
Faculty of Veterinary Sciences
University of Utrecht
P.O. Box 80158
Utrecht
The Netherlands

J. G. Vos
Laboratory for Pathology
National Institute of Public Health and
Environmental Hygiene
P.O. Box 1
3720 BA Bilthoven
The Netherlands

Preface

A symposium was held in September 1985 at the University of Kent to mark the retirement of Dr W. Norman Aldridge, the Deputy Director of the Toxicology Unit of the Medical Research Council and the first Chairman of the British Toxicology Society. The title of the Symposium was *Selectivity and Molecular Mechanisms of Toxicity* and it was intended to highlight the major guiding principles in Norman's distinguished scientific career which made him a recognised pioneer of toxicological research both in the UK and worldwide. Most of the contributors had been closely associated with Norman, either as students or as collaborators, and we were very happy to organise the scientific programme with the help of Martin Johnson, which we gratefully acknowledge.

This book is aimed at providing a more permanent tribute to Norman's influential achievements. It is a collection of short reviews which have been written by the contributors to the symposium, all specialists in various fields of human and experimental toxicology, and which illustrate some of the most interesting and topical problems in present-day toxicological research. Examples are given of the molecular basis for tissue-selective toxicity in the lung, peripheral nerves, kidney and immune system; and the mechanisms of toxicity of toxic lectins, organophosphate inhibitors, genotoxic chlorinated hydrocarbons and suicide substrates of cytochrome P-450 are then considered. Finally, human and experimental studies on the toxicity of three classes of compounds (MPTP, hexane and impurities of commercial parathion) are reviewed: these have received a great deal of interest in recent years for their involvement in human toxicity, being associated with the development of previously undescribed toxic syndromes.

Our thanks go to the British Toxicology Society who supported the symposium and encouraged the publication of this book.

Carshalton and Alderley Park, 1987

F. De M.
E. A. L.

Part I

Tissue-selective Toxicity

1
Cellular Specific Toxicity in the Lung

Lewis L. Smith and Benoit Nemery

INTRODUCTION

The architectural structure of the lung is designed to provide and protect a vast surface area within the chest cavity which allows the effective exchange of respired gases with the bloodstream. This means that the lung has numerous cell types with specific functions and when the cell types in the blood are taken into consideration, over forty individual cell types have been identified (Sorokin, 1970). Since the total cardiac output passes through the lung, the lung can be exposed to toxic xenobiotic compounds and their metabolites present in the blood. The lung is also exposed to gases, vapours and particles (if small enough) present in the inspired air. Even toxins present at very low concentrations in the atmosphere may present a risk to the lung, especially when one considers that the adult human lung respires approximately three tons of air per year (Mustafa and Tierney, 1978).

The selective vulnerability of lung cells will depend on several factors. These will include:

1. The route of exposure (i.e. inhalation or via the bloodstream).
2. The mean aerodynamic diameter (particulates).
3. Solubility of inhaled gases (e.g. sulphur dioxide compared with ozone).
4. Selective uptake mechanism (e.g. paraquat).
5. Selective metabolic activation (e.g. 4-ipomeanol).
6. Susceptibility of individual cell types.
7. Species susceptibility (e.g. butylated hydroxytoluene, BHT; trialkylphosphorothioates; α-naphthylthiourea, ANTU; 4-ipomeanol; paraquat).

It is the purpose of this review to consider in some detail the mechanism of toxicity of some chemicals which damage the lung. In doing so we shall attempt to highlight the cellular specific toxicity which these chemicals provoke. In particular we shall